Streptococcus milleri pulmonary disease: a review and clinical description of 25 patients

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Abstract

***Background* – *Streptococcus milleri* is increasingly being recognised as an important pulmonary pathogen which may lead to the development of empyema or lung abscess. Although several small series have been reported, the clinical and laboratory features have yet to be fully characterised.**

***Methods* – Twenty five cases were identified and the clinical and laboratory data from case records were analysed.**

***Results* – There were 16 empyemas, five lung abscesses, and four with both lung abscess and empyema. The mean age of the patients was 61 years (range 36–89) and 84% were men. The most common symptoms at presentation were shortness of breath, chest pain, cough, and weight loss; only 36% had a fever. Four of the nine patients with lung abscess required a diagnostic lobectomy because of suspected malignancy. Predisposing factors were present in 80% of patients and included the following: pneumonia, periodontal disease, excess alcohol intake, previous thoracic surgical procedures, and malignancy. Laboratory features of *S milleri* infection were leucocytosis, neutrophilia, anaemia, abnormal liver function tests, and hypoalbuminaemia. In the group with empyema five patients had a pneumothorax on initial presentation and pleural loculation occurred in 10 of these patients. The median stay in hospital was 34 days (range 11–88). Six patients died, five of whom had significant underlying illnesses.**

***Conclusions* – Pulmonary infection with *S milleri* may result in considerable morbidity and mortality, and is characterised by a strong male predominance, non-specific symptoms (often without toxicity), the presence of predisposing factors, pleural loculation, pneumothorax, and a protracted stay in hospital.**

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Keywords: *Streptococcus milleri*, empyema, lung abscess.

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The term "*Streptococcus milleri* group" refers to a heterogeneous group of streptococci which is increasingly being recognised as a group of clinically important pathogens. The classification of these organisms has been the subject of considerable debate with the emergence of British and American systems.[1] The British system[2] groups the organisms into one species, *Streptococcus milleri*, while the American system[1,3] separates them into distinct species (*Streptococcus anginosis*, *Streptococcus constellatus*, *Streptococcus intermedius*). Two more recent modifications of these systems have been described – one[4] supports a single species (*Streptococcus anginosis*) and the other[5,6] supports a separation into three species. Despite these taxonomic differences, the term "*Streptococcus milleri*" has persisted and is widely used in the clinical setting. Two other terms – "viridans streptococci" (which includes other streptococcal species) and "microaerophilic streptococci" – are also used by a number of laboratories to refer to *Streptococcus milleri* but do not identify the organisms to a species level.

Streptococcus milleri is a widely distributed commensal which is normally found in the mouth, upper respiratory tract, gastrointestinal tract, and vagina.[7] Various pyogenic infections have been attributed to this pathogen which has a striking predilection for abscess formation. It is a recognised cause of brain, dental, lung, liver, subphrenic, pelvic, and subcutaneous abscesses, as well as abscesses in other sites. It may also cause empyema, meningitis, osteomyelitis, peritonitis, and endocarditis.[8–12]

There are a number of reports documenting the importance of *S milleri* in the development of empyema and lung abscess. However, only five small series describe the clinical features in these patients. Shlaes *et al* found six cases of empyema (three associated with lung abscess) and one case of lung abscess alone over a 10 year period.[9] A series from New Zealand reported four cases of empyema in six months.[13] Hocken and Dussek[14] reported six cases of empyema in a consecutive series of 25 patients in one year and Ferber *et al*[15] found 11 patients with empyema in one year and described six cases. Another more recent series from Japan described 10 cases of empyema over a five year period.[16]

We report the characteristics of 25 patients with *S milleri* infection associated with empyema or lung abscess.

Methods

Twenty five patients with empyema and/or lung abscess due to *S milleri* are described. Twenty two cases were identified from the microbiology department computer records of all *S milleri* specimens from two 1400 bed general hospitals (City and University Hospitals, Nottingham) between October 1991 and September 1994. Three additional patients identified before this period were included in the analysis. Specimens were obtained by thoracocentesis, thoracotomy, and at necropsy in one patient. Med-

Table 1 Clinical characteristics, management, and outcome in 25 patients with S milleri empyema or lung abscess

Patient no	Age (yrs)	Sex	Abscess (A) or empyema (E)	Predisposing factors†	Associated organisms	Treatment§	Days in hospital	Outcome
1	60	M	A		Nil	Lobectomy‡	30	R
2	89	M	A	Pneumonia	Nil	Nil	17	D
3	36	M	A	Dental caries and periodontal disease	Nil	Lobectomy‡	22	R
4	42	M	A	Dental caries and periodontal disease	Nil	Lobectomy‡	57	R
5	64	M	A	Pneumonia	Nil	Percutaneous catheter drainage	77	R
6	51	M	E	Pneumonia, NIDDM, thoracoscopy	Nil	Intercostal tube drainage, open drainage + rib resection	27	D
7	58	M	E	Spontaneous pneumothorax, intercostal tube drainage, thoracotomy	*Staph aureus* coliform bacilli	Intercostal tube drainage	35	R*
8	59	M	E	Excess alcohol	Nil	Open drainage + rib resection	34	R
9	41	M	E	Pneumonia	*Bacteroides* sp	Open drainage + rib resection	11	R
10	49	F	E	Pneumonia, excess alcohol	Anaerobes	Open drainage + rib resection	41	R
11	80	M	E		Nil	Intercostal tube drainage	31	R
12	56	M	E	Pneumonia, excess alcohol	Nil	Needle aspiration	11	R
13	63	F	E	NIDDM	Nil	Open drainage + rib resection	12	R
14	73	M	E	Pneumonia, dental caries and periodontal disease	Anaerobes	Intercostal tube drainage	44	D
15	64	M	E	Pharyngeal pouch, aspiration pneumonia, oral steroids, dental caries and periodontal disease	*Bacteroides* sp	Intercostal tube drainage	73	R*
16	67	M	E	Lung carcinoma, lobectomy	Coliform bacilli	Intercostal tube drainage	26	D
17	83	M	E	Oesophageal perforation	*P aeruginosa*	Intercostal tube drainage	85	R
18	77	M	E	Bladder carcinoma	Nil	Intercostal tube drainage, open drainage + rib resection	49	R
19	61	M	E	Pneumonia	Enterococci, anaerobes	Intercostal tube drainage	30	R
20	76	M	E	Pneumonia, stroke	Nil	Antibiotics only	9	D*
21	55	F	E	Subphrenic abscess	*E coli*, *Actinomyces* sp, anaerobes	Needle aspiration, intercostal tube drainage	88	R
22	62	M	E, A		Nil	Intercostal tube drainage	36	R
23	57	M	E, A		Nil	Lobectomy‡, open drainage + rib resection	34	R
24	44	F	E, A	Pneumonia, lung carcinoma, dental caries and periodontal disease	Nil	Intercostal tube drainage	41	D
25	52	M	E, A		Nil	Intercostal tube drainage	21	R

* Admitted to the intensive care unit.
† Pneumonia refers to primary community acquired pneumonia.
‡ Diagnostic resection of lung abscess.
§ Not including appropriate antibiotics.
D = died; R = recovered; NIDDM = non-insulin dependent diabetes mellitus.

ical records were reviewed using a standard data collection form.

Specimens were directly examined using the Gram stain and then plated onto a range of non-selective and enriched media for aerobic and anaerobic incubation. The plates were incubated at 37°C for up to five days. Any colonies with the colonial appearance and typical caramel odour of *S milleri* were subcultured to check for enhanced growth in carbon dioxide and were Lancefield grouped using a rapid latex test (Oxoid Streptococcal Grouping Kit, Unipath Ltd). The classification scheme of Colman and Williams for viridans streptococci was used.[2]

Results

Streptococcus milleri pleuropulmonary infection was identified in 25 patients (16 empyemas, five lung abscesses, and four with both lung abscess and empyema). Six patients died. The median age was 60 years (mean 61; range 36–89); 21 of the patients (84%) were men.

The median duration of symptoms in 24 of the patients was 18 days (mean 61; range 1–300). In addition, one patient (no. 6) had protracted symptoms (730 days) because of difficulty in establishing a diagnosis, and subsequently died. Nine patients had symptoms for more than three months before presentation and only five patients had symptoms for less than one week. The most common symptoms at the time of presentation were shortness of breath (76%), chest pain (72%), cough (64%), and weight loss (40%). Other symptoms included fever (28%), sweats (16%), haemoptysis (12%), and rigors (4%). Twenty patients were cigarette smokers.

Only nine patients had a fever at presentation of >37·5°C; however, 20 patients had a fever of >37·5°C during the admission. Clubbing was found in eight patients.

Community acquired pneumonia was associated with the development of empyema or lung abscess in 10 patients (table 1). Dental caries and periodontal disease was noted in four patients; in the other patients this information was not available. Three had a history of excessive alcohol intake. Three patients had previously had thoracic surgical procedures, one patient had a perforated oesophagus which was treated conservatively, and one had a subphrenic abscess. Three patients had carcinomas (two lung, one bladder), two patients had diabetes mellitus, and one had a dense hemiplegia associated with a stroke. One patient was taking oral corticosteroids and no patients were taking other immunosuppressive medications. Overall, a predisposing factor was present in 20 patients.

Streptococcus milleri was grown from pleural fluid (19), resected lung (four), postmortem pleural fluid and lung (one), and lung aspirate (one) in pure culture in 16 of the 25 patients and anaerobic organisms were also cultured in six patients (table 1). Sputum cultures were obtained in 21 patients and *S milleri* was cultured from only one specimen (pleural fluid positive also). One patient with empyema also

Table 2 Results of laboratory studies on presentation in 25 patients with S milleri infection

*Test**	*Number (%)*	*Median*	*Mean*	*Range*
White cells ($\times 10^9$/l)		14·5	17·1	7·3–42·3
<11	5 (20)			
11–15	9 (36)			
>15	11 (44)			
Neutrophils ($\times 10^9$/l)		12·8	14·2	4·3–38·6
>7·5	19 (76)			
Haemoglobin (g/dl)		11·6	11·2	8·2–15·5
<13 (M) or <11·5 (F)	19 (76)			
<10	7 (28)			
ESR (mm/hour)	(6 cases measured)	96	90	32–124
Urea (mmol/l)		5·9	9·0	3·4–29·7
>6·5	8 (32)			
Albumin (g/l)	(22 cases measured)	31	30	13–45
<30	10 (45)			

* Normal values: white cells 4–11 $\times 10^9$/l; neutrophils, 2–7·5 $\times 10^9$/l; haemoglobin 13–18 g/dl (M); 11·5–16·5 g/dl (F); urea, 2–6·5 mmol/l; albumin, 30–48 g/l.

grew *S milleri* from a subphrenic abscess. Blood cultures were obtained in all 20 patients who developed a fever of >37·5°C and none grew *S milleri*. All the *S milleri* isolates were sensitive to penicillin.

At the time of admission the white cell count was raised in 20 patients (80%), the neutrophil count was raised in 19 patients (76%), and the haemoglobin was low (<13 g/dl M, <11·5 g/dl F) in 19 patients (76%). Seventeen of the 19 patients (89%) in whom liver function tests were measured had abnormal results. Of 22 patients with albumin levels measured at the time of presentation, 10 (45%) were less than 30 g/l (table 2).

Chest radiographs or computed tomographic scans during the hospital admission showed loculation in 10 of the 20 empyemas. Of the 20 empyemas, 13 occurred on the left, as did four of the nine lung abscesses. In five of the empyemas pneumothorax was present on the initial chest radiograph (prior to needle aspiration). Another patient developed empyema complicating spontaneous pneumothorax.

All patients received antibiotics except patient no. 2 in whom the diagnosis was made at necropsy. Patients received a variety of antibiotics because of early empirical treatment; 23 of the 24 patients received benzylpenicillin, ampicillin, amoxycillin, amoxycillin plus clavulanic acid, or cefotaxime following isolation of *S milleri*. In the group with empyema 13 patients were managed by antibiotics and intercostal tube drainage (table 1) and two patients subsequently required open drainage. Five patients had open drainage as first choice treatment. In the nine patients with lung abscess four had a diagnostic lobectomy and one patient was treated with a percutaneous catheter.

The median duration of stay in hospital for the 19 surviving patients was 34 days (mean 41; range 11–88). Three patients (nos 7, 15, 20) were admitted to the intensive care unit for 24, 35, and nine days respectively. Of the six patients tho died, five had underlying illnesses (two lung cancer), one diabetes, one stroke, one rheumatoid arthritis. Patient no. 2 was diagnosed at necropsy and received no specific treatment. All of the deaths were directly attributed to the underlying *S milleri* infection. There was no relationship between death and the clinical, laboratory, or radiological features.

Discussion

Pulmonary infection with *S milleri* in our series was characterised by a male predominance, leucocytosis, abnormal liver function tests, pleural loculation, a high incidence of pneumothorax, and a protracted stay in hospital. Previous reports have noted the presence of severe toxic symptoms and rapid onset and progression, but these features were not prominent in our cases and the disease was often indolent.[13 17] In four of the nine patients with lung abscess lung resection was performed because malignancy was suspected, and none of these patients had toxic symptoms or fever on presentation.

Predisposing factors which have been associated with *S milleri* empyema and lung abscess include mucosal disturbance (sinusitis, periodontal disease, enteric disease such as oesophageal perforation), preceding pneumonia, thoracic surgery, malignancy, neurological disease, alcohol abuse, and diabetes.[9 13–17] In our series predisposing factors were present in 80% of cases, with pneumonia occurring in 40% of the empyemas and thoracic surgery in 15%. This compares with 67% in an extensive review of *S milleri* infections at any site.[12] In empyema caused by other organisms, pneumonia accounted for about 50% of cases and another 25% were due to thoracic or gastro-oesophageal surgery.[18 19]

Pure culture occurs in 30–83% of patients with *S milleri* pleuropulmonary infection and mixed culture with anaerobes in 17–60%.[9 11 13–16 20] *S milleri* was isolated in pure culture in 64% of our patients and in mixed culture with anaerobes in 24%. These anaerobic organisms, which include *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella*, are members of the oral flora and their presence in association with *S milleri* infections suggests an oropharyngeal source of infection. They may also have a role in promoting *S milleri* infection by delaying clearance, enhancing growth, and inhibiting bactericidal activity of neutrophils.[21] Although the pathogenic mechanisms involved in *S milleri* infections have yet to be fully elucidated, *S milleri* is known in some isolates to produce enzymes such as hyaluronidase, DNase, gelatinase, collagenase, and an immunosuppressant substance.[22–25] Anaerobic organisms may also produce extracellular enzymes and it has been proposed that these could act in concert with enzymes produced by *S milleri* in causing tissue damage and spread of infection.[21]

The characteristic features of pleuropulmonary disease caused by *S milleri* do not reliably distinguish it from pleuropulmonary disease due to other organisms. In a review of series of empyema reported between 1980 and 1991 the most common predisposing factor was pneumonia, the average hospital stay varied between 12 and 56 days, and mortality ranged from 0 to 51%.[26] Several differences, however, can be noted. Firstly, in empyema due to *S milleri* pleural loculation is common while loculation occurs rarely in pneumococcal empyema.[26] Secondly, the high incidence of pneumothorax noted in our series is unusual,

and suggests that empyema arose by rupture of a peripheral lung abscess.

The key principles of management of *S milleri* infection are early diagnosis, control of the infection with appropriate antibiotics, and adequate drainage. During the assessment of patients it is important to be aware that toxic symptoms may be absent and that lung abscess may mimic malignancy. Periodontal disease appears to be an important predisposing factor which may be underestimated and all patients should have a careful examination of the mouth and teeth. The antibiotic of choice is intravenous penicillin, although the organism is also susceptible to ampicillin and cephalosporins. For patients allergic to penicillin, suitable alternatives are erythromycin, clindamycin, or vancomycin.[12] If empirical treatment is necessary, metronidazole should be added to cover for anaerobic organisms. For empyema, drainage is usually achieved by closed methods but open surgical drainage may be required and often represents chest tube failure or delayed presentation. The principle of early space drainage in the management of empyema has been questioned in a recent study.[27] However, no cases of *S milleri* were reported in the study and further evidence is required before delaying or withholding drainage. Recently there has been increased interest in the use of intrapleural streptokinase to facilitate drainage and, with the development of purer formulations, this appears to be safe and effective.[28 29] This form of treatment may be particularly suitable for *S milleri* infections because of the frequent occurrence of loculation.

Although the incidence of empyema or lung abscess caused by *S milleri* is low, infection is associated with considerable morbidity and mortality. Patients often have a complicated course in hospital and may consume considerable resources during their management. It is therefore important that patients are managed aggressively with a view to early and accurate diagnosis, antibiotics, and appropriate drainage.

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